--28. A method of treating a mammal having polycystic breast disease, comprising administering to said mammal in need thereof, an amount of a pharmaceutical composition, comprising a targeted chimeric toxin as claimed in claim 1, sufficient to ameliorate the effects of said polycystic breast disease.

REMARKS

Reconsideration of the patentability of the claims of the above identified patent application is solicited in view of the above amendments and the following comments.

It is believed that the fee filed herewith is the complete fee that is due with the filing of this response. However, if any additional fee is required, kindly charge the same to the undersigned attorneys' deposit account 07-1337. It is believed that the extension of time petitioned for in connection with this response is sufficient to maintain the pendency of this application. However, if any further extension of time is required to maintain the pendency of this application, kindly consider this to be a petition therefore.

In paragraph 2 of the outstanding action, the examiner has complained about the format of new claim 22. He has objected to the Markush group on the basis that its several members are alleged by him to be patentably distinct. While it is true that the examiner has ruled that the several members of the Markush group are patentably distinct, that does not militate against the propriety of this type of sub-generic claim. Sub-generic Markush group claims have always been accepted as proper even when the members thereof are patentably distinct. The criterion for propriety of a Markush group is whether the members have a commonality in regard to the claimed invention. In the instant case, the members of the Markush group are all diseases that are treatable with the compounds of this invention. Having satisfied that criterion, the Markush group is proper and should be treated as would any other sub-generic claim that embraces species

that may be patentably distinct from each other and/or from their genus. It is urged that the examiner reconsider and withdraw this objection. It is noted that claim 22 is now completely generic.

In the previous action, the examiner has issued what was denominated a restriction requirement. However, in reality it was an election of species requirement. While applicants have made their election to immediately prosecute the claims embraced by Group I as identified by the examiner, this was not acquiescence to the outstanding requirement being one of restriction. The claims elected for immediate prosecution are 1-7, 9, 10, 21 and 22, but this election was and is against an election of species requirement, not a restriction requirement. The several groups of claims identified by the examiner as pertaining to patentably distinct inventions are all species of a single encompassing inventive concept. The fact that the several species may be patentably distinct from each other does not mean that the generic invention is not a patentable umbrella under which each of these patentably distinct species falls. These claims are generic to claims to the species that was elected for immediate prosecution. Applicants are therefore entitled to have these claims prosecuted along with the claims to the elected species. In the unlikely event that the examiner finally holds that the claims to the elected species are unpatentable, he will then be entitled to reject the generic claims on the same basis. In the event that he finds the elected species covered by the elected claims patentable, the examiner will then be obliged to examine the remaining species claims, in turn if he sees fit, and upon finding each of these species patentable, he is obliged to also allow the generic claims. For this reason, claim 22 belongs with the elected species claims and should be prosecuted at the same time, at least to the extent that they cover the elected species.

The examiner's comments in paragraph 5 of the outstanding action are not understood. In response to an election of species requirement, applicants elect a single species for immediate prosecution. Contrary to the situation that results in a restriction requirement where no generic

claim can be written to embrace the several patentably distinct inventions that are being claimed, in the case of multiple claimed species, it is possible to write a proper generic claim, and instant claim 22is such a claim. The non-elected claims are not to be canceled, but examination thereof is merely deferred pending conclusion of examination of the elected species. The examiner's requirement for cancellation of the non-elected claims is therefore objected to, and traversed. It is agreed that these non-elected claims are withdrawn from immediate consideration, but it is not agreed that they will not eventually belong in this application.

The requirements of paragraph 7 have been complied with. Please see the above amendments to the specification.

The requirements of paragraph 8 relating to the drawing have been considered. In order to comply with the examiner's suggestions, the six (6) sub-figures of figure 3 have been cut apart and are presented attached hereto, one to a page each with its proper axis labels. No substantive change has been made to any of these figures. Note that figures 2A and 2B suffered from the same axis identification problem as the sub-figures of figure 3. This too has been corrected as shown on the attached sheets of drawings. No substantive change has been made in figure 2 either. The number of pages of drawing has been increased, however, to 13. Therefore, there is being submitted a new set of 13 pages of drawings, with each page newly numbered as a function of these 13 sheets. It is urged that the examiner consider this submission and approve it. It is recognized that, when this application is allowed, the formal drawings as well as appropriate photographs will need to be submitted. Action on these submissions is respectfully deferred pending allowance.

The claim objections set forth in paragraph 9 of the outstanding action have been considered and the above amendments should obviate the objections set forth in sub-paragraph b. In claim 2, there should be no comma after "uterine". Claim 22 is not required to be withdrawn

or canceled as it is a proper generic claim with respect to the elected species. Sub-paragraphs a and c have therefore not been addressed by amendment. It is urged that the examiner withdraw the objections raised in these sub-paragraphs. If the examiner still has concerns for the claim language and format, he is requested to telephone the undersigned attorney to discuss the remaining problems. Every effort will be made to accommodate the examiner's concerns.

In paragraph 10a of the outstanding action, the examiner has objected to the use of the term "fused" in the expression "targeted fused chimeric toxins" that appears in the claims. In the context of the instant patent application, the term "fused" clearly means two DNA fragments ligated together. As such, it is an entirely appropriate word used by the applicants in its correct manner. Further, this term is being used to differentiate between ligated DNA fragments and chemically reacted functional groups of different chemical compounds. Still further, since applicants are entitled to be his own lexicographer, and the term is being used in its correct context, it is believed that this term should be retained in its current usage.

In paragraph 10b of the outstanding action, the examiner has objected to the use of the term "produced by genetic engineering techniques" that appears in the claims. In the context of the instant invention, this term means that the entire chimeric toxin has been produced by generic engineering techniques. That meaning is entirely consistent with everything that has been disclosed in the instant specification as originally filed. As will be pointed out in more detail below, the manner in which the claimed compounds are made is critical to the efficacy of this invention. The compounds of this invention are "reaction products" of other compounds. How these reactants are joined together makes a great difference in the efficacy of the product that results. Therefore, the method of making (produced by genetic engineering techniques) is a critical limitation on the claimed product. It is urged that the examiner reconsider and withdraw this objection.

In paragraph 10c of the outstanding action, the examiner has objected to the use of the terms "toxins" and "moieties" because of their plural aspect. This position of the examiner is respectfully traversed. These terms are intentionally directed to their plural aspects. This invention is directed to a plurality of chimeric proteins. All of these proteins comprise gonadotropin releasing hormone (GnRH), or analogs thereof, as the targeting moiety, fused, at the cDNA level, to various forms of the PE toxin as the killing moiety. In the instant specification, there is a disclosure of one specific analog of GnRH in which trp replaces gly at amino acid No. 6. There is also disclosed a mutated PE ($PE^{64glu}$) and a truncated PE from the $PE^{40}$.

In paragraph 10d of the outstanding action, the examiner has objected to the claims as being unclear as to whether the cell killing moiety or the cell targeting moiety recognizes the cell. Please refer to amended claim 1 above. It is believed that the revised language should make it clear that the targeting moiety recognizes the cell and the killing moiety destroys the targeted cell. Withdrawal of the objection is solicited.

In paragraph 10e of the outstanding action, the examiner has objected to claim 2 as having improper Markush group language. Reference is made to amended claim 2 above. It is believed that these amendments obviate this objection. Withdrawal of this objection is solicited.

In paragraph 10f of the outstanding action, the examiner has objected to the language of claim 3 with respect to the term "mutated". The examiner is questioning whether a person of ordinary skill in this art would know from the claims what mutations are intended. This position of the examiner is respectfully traversed. The claims define the metes and bounds of the invention. They are not the teaching portion of the patent. Rather, the specification is the teaching portion of the patent. This specification amply teaches which mutations illustrate the operation of this invention. The specific mutations set forth in the specification are too limiting

to be placed in the claims. To limit claim 3 in the manner apparently suggested by the examiner would so unduly restrict the scope of the claim as to make it easily avoidable while practicing the substance of this invention with impunity. A person of ordinary skill in this art, upon reading the instant specification that illustrates this feature of the invention with a specific mutation, will certainly be able, with a minimum of experimentation, to duplicate the invention and to extend the exemplified form of the invention to its reasonable equivalents. This objection is therefore traversed and it is urged that it be withdrawn.

In paragraph 10g of the outstanding action, the examiner has indicated that, in his opinion, it is unclear what entity in claims 3 and 4, the sequence or the exotoxin, encodes the protein GnRH-PE40. It is clear that the exotoxin having the specified sequence is what encodes the protein. The examiner's objection is not understood. Perhaps the examiner would be so kind as to specify what language he would like in place of what is in the existing claims. Applicants will give every consideration to any suggestion that the examiner may wish to make in regard to rearranging the language to obviate his objections.

In paragraph 10h of the outstanding action, the examiner has objected to the language of claims 5, 6 and 9. Reference is made to the above amendments that are believed to obviate these objections. Should the examiner continue to have objection to these claims, he is requested to telephone the undersigned attorney with suggestions.

In paragraph 10i of the outstanding action, the examiner has objected to the language of claims 5, 6, 9, 10 and 22. Reference is made to the above amendments that are believed to obviate these objections. Should the examiner continue to have objection to these claims, he is requested to telephone the undersigned attorney with suggestions.

In paragraph 10j of the outstanding action, the examiner has objected to the language of claims 5 in relation to the term "mutated form of PE". The instant specification discloses an example of a mutated PE ($PE^{64glu}$). With this information at hand, a person of ordinary skill in this art can, with a minimum of experimentation, determine which other mutations will suffice for the purpose at hand. It is urged that the examiner reconsider his position and withdraw this objection.

In paragraph 10k, the examiner has objected to the term "patient's body" in claim 9. The examiner's position is respectfully traversed. However, in order to expedite the prosecution of this application, the above amendments have deleted this term from the claim. Withdrawal of this objection is therefore solicited. It is submitted that this deletion does not introduce any prosecution history estoppel as it has been done for purposes other than to avoid claiming subject matter that is within the state of the prior art.

In paragraph 10l of the outstanding action, the examiner has objected to the use of the term "analog" in claims 3-6. In the instant specification an example is given of one such analog that is the sequence where trp replaces gly as the sixth amino acid. This example coupled with the entirety of the specification will lead one of ordinary skill in this art to determine the scope of the analogs referred to in the claims with a minimum of experimentation. It is urged that the examiner withdraw this objection.

In paragraph 10m of the outstanding action, the examiner has objected to the use of the term "sequence" in claims 3 and 4. Reference is made to the above amendments of these claims that should obviate this objection.

In paragraph 10n of the outstanding action, the examiner has objected to claims 3-6 for reciting the proteins GnRH-PE66 and GnRH-PE40 rather than identifying them by sequence ID

Nos. This objection is respectfully traversed. Reference is made to Fig. 1C where the sequence corresponding to GnRH-PE66 is shown. It will be clear to a person of ordinary skill in this art that, given the disclosure in this specification, there will be no mistake as to what protein is being described using the referred to indicia. Withdrawal of this objection is solicited

In paragraph 10o of the outstanding office action, objection has been raised to the use of the terms GnRH and PE in claims 3-6 without first defining what these abbreviations stand for. Reference is made to above amended claims 3 and 4 where this problem has been addressed. It is urged that the examiner withdraw this objection. The amendments to claims 3-6 in regard to overcoming this specific objection do not raise prosecution history estoppel. The amendments have been made for format purposes and have nothing to do with the state of the prior art.

In paragraph 10p of the outstanding office action, the examiner has raised objection to the language of claims 5 and 6. Reference is made to the above amendments that are believed to obviate the examiner's objections. Withdrawal of these objections is therefore solicited. The amendments have been made for format purposes and have nothing to do with the state of the prior art.

It is pointed out that the above amendments to the several claims of this application have been made in consideration of the various formal objections to claim language that the examiner has raised. They are **not** for the purpose of avoiding the application of any prior art or for reducing the scope of the claims. Therefore, these claim amendments do not raise any prosecution history estoppel issues, and nothing contained in this response should be considered to do so.

In paragraphs 12a-j of the outstanding action, the examiner has objected to all of applicants' claims on the basis that the specification has limited enablement and does not support

the scope of at least some of the claims. It is noted that the examiner has acceded to the fact that the subject matter of claims 3, 4, 5 and 6, as well as claims dependent therefrom are not subject to this objection because they contain reference to the specific materials the examiner has conceded are specifically disclosed in this application. More importantly, the claims of this application are not directed to full length native, unmodified Pseudomonas Exotoxin. Such a protein without any modification is admitted to bind to almost every mammalian cell and therefore is not capable of achieving specific targeting of cancer cells. The instant invention is concerned only with PE that has been modified, either by mutation or by truncation. Truncated PE according to this invention can be for example PE from which domain I has been excised. The preferred mutated form occurs when the mutations are accomplished in domain I. PE in its full length, native form is not encompassed by the instant claims nor is it considered to be part of the instant invention.

While it is true that the amino acid sequence of a protein determines its structural, and therefore its functional, properties, it is also well known and well documented that proteins can tolerate many changes in their sequence, including ligating them with other proteins, that may be quite large, in either their $NH_2$ or their COOH terminus, and still retain their specific biological properties.

This specification shows that GnRH analog can be ligated to a large protein fraction (PE66) and still retain its biological activity and selectivity. This shows that this protein can be further modified and it is reasonable to expect that it will still retain its desired properties. In any case, modification of proteins is a well known science at this stage of the technical development. Only a minimum of experimentation will be required to determine just how far the changes can go before the resulting molecule loses its desirable biological activity and selectivity. It is also pointed out that the specific protein exemplified in this application has literally thousands of known analogs. To the best of applicants' knowledge and information, all of these analogs have

retained the known biological activity that is generally attributed to this protein insofar as this invention is concerned. It is not unreasonable to believe that this property will continue to exist with other analog modifications.

It is now known that GnRH-toxin chimeric proteins can target and kill adenocarcinoma cells in mammals. These include: colon, breast, prostate, ovarian, endometrial, renal and liver cancer cells, which are all of the adenocarcinomal form. This is because adenocarcinoma cells all express the GnRH binding site and thus can be targeted and killed according to this invention. Therefore, it is also apparent that the treatment of this invention is specific to the various mammalian adenocarcinoma cancer cells and does not effect other types of cancers. It is believed that the reason for this selectivity is that the compositions of this invention all share the same characteristics of (over) expressing the GnRH binding site. Note the amendments to the claims regarding the kinds of cancers against which the instant invention is effective. It is therefore urged that the examiner reconsider and withdraw this objection.

In paragraphs 12k-n of the outstanding action, the examiner has objected to the patentability of the instant application on the basis that there are the known impediments to drug delivery in cancer situations and the lack of a specific example of the *in vivo* treatment of a cancer. There are also other related objections. While it is certainly true that there may be a quantum leap between laboratory and clinical efficacy, the instant invention has been shown to be useful, which is the statutory criterion required to support patentability. The examiner must remember this is not an FDA investigation. It is an evaluation of the disclosure of an invention under the auspices of 35 USC 112. The statute requires utility, novelty, and non-obviousness. The instant invention satisfies these criteria, whether there have been clinical trials or not.

It is acknowledged that sometimes drugs that have been shown to be effective in animal trials are not effective with human patients. This is true of cancer combating drugs as well as

other drugs. In the instant case, however, there is a substantial amount of evidence that support the proposition that the instant treating agent will be effective with humans as well as other mammals. In order to go on with the further research and trials needed to show the efficacy of the instant drug in fighting cancer and other diseases, one must first overcome the hurdle of obtaining the fundamental information that the instant patent application is based on. Studying the *in vivo* effect of drugs gives the researcher the first line evidence of the efficacy of a drug. Without this evidence, nothing further can be done. Most importantly, without this evidence and a patent, there is very little likelihood of further financial support. The data reported in this specification are based on models that have been well accepted in the scientific community. The results of these tests determine whether further testing is appropriate. The data in this application show that the specific drugs, to which this invention is directed, are efficacious, at least at the level of testing that has so far been conducted. That is sufficient to support patenting. Without patenting, it is unlikely that the next level of investigation will ever get off the ground for lack of funding.

The instant specification is certainly sufficiently complete to comply with the requirements of 35 USC 112. It amply describes what the claimed product is and the fact that it combats adenocarcinomas. It describes the effects of a targeted chimeric protein on various cell lines (see example 4). . It describes the effects of a targeted chimeric protein on various primary cultures (see example 5). The examples show the selectivity of the claimed material. The claimed targeted chimeric protein is novel and unobvious. It is useful at least for selectively killing certain adenocarcinoma cell lines. It therefore satisfies the criteria for patentability.

The objection based on the allegation that the specification does not disclose a method of formulating the instant claimed compositions into a pharmaceutical composition is simply not understood. The examples in this application apply a pharmaceutical composition to certain cell lines, among other things. Certainly that pharmaceutical composition must have been made up.

Further, and more importantly, the assembly of new drug into a pharmaceutical composition is a widely well known technology. There is nothing that suggests that the agents of this invention would be put up in a pharmaceutical composition in any form that is substantially different from what is known technology in this field. More importantly, it is the composition that is specified in the claims and its use against adenocarcinomas that distinguishes this invention from the state of the prior art.

It is urged that all of the objections under 35 USC 112 be withdrawn in view of the comments and amendments that have been submitted herein.

In the outstanding action, the examiner has rejected the patentability of claims 1, 2 and 7 as being anticipated by the disclosure of the Nett et al. publication. The examiner has contended that this reference discloses conjugation of GnRH with toxins, where the GnRH is used to target cells bearing GnRH binding sites and the toxin is used to permanently destroy the targeted cells. Further, the examiner has contended that the manner of making the claimed product and the use to which it is intended to put the product do not reflect on the patentability of the product. Therefore, it is the examiner's asserted position that this reference anticipates the instant claimed invention.

With respect, applicants disagree with the examiner. In the first place, while it is generally true that the method of making a specific claimed product does not lend patentability to that product, that is not the case where the product, even though known by the same name, but made by the different methods, differs in some material aspect. In the case at bar, the reference conjugates GnRH with a purported toxin by chemical reaction according to the well known techniques of organic chemistry. The product of such conjugation is a mixed bag. It contains many different reaction products because the toxins have many different ligand attachment sites, such as amino groups and carboxy groups. This type of chemistry is not selective of the number

or place of GnRH molecules that are activated and attached to the toxin. Thus, the final product of such chemical conjugation of the GnRH and the toxin is a mixture of many compounds.

To the contrary, by using genetic engineering techniques, the product of the instant invention is a very pure single fused compound. The fusion occurs at the cDNA level, which is not what is disclosed by the reference. Thus, although in many cases the manner of preparation of a material is not pertinent to its novelty with respect to another compound that is nominally of the same name but has been prepared in a different manner, that is not the situation here because the compounds prepared according to the reference and according to the instant invention are in fact different even though the same nominal reactants are employed to make them.

While it is also true that the intended use of a claimed product does not lend patentability to that product, the discovery that a certain product (in this case the specific product that results from it having been made in a certain manner) has unexpected, and therefore unobvious, properties/uses is evidence that the claimed product is different, unobviously so, from the compounds made by the techniques disclosed in the reference, and is therefore patentable. In this case, the instant claimed compounds have been found to be effective against mammalian carcinomas that originated in non-hormone dependent tissues, such as colon, lung, renal and kidney carcinomas. The compounds disclosed by the reference have only been reported to be effective against sex steroid dependent tumors. Therefore, the instant claimed materials are both different, they are novel, and have unexpected properties, they are unobvious. Certainly, they are useful. It is believed that the limitation in the claims of how these claimed products are made is a material and significant one. The reference does not meet this limitation and therefore the rejection under 35 USC 102 must be withdrawn. For the reasons set forth above, no obviousness based rejection should be made either.

Further, there is a substantial difference in the manner in which the reference material acts and the manner in which the instant claimed material kills carcinoma cells. According to the reference, its product acts indirectly by attacking the gonadotropin-releasing cells of the anterior pituitary gland because those are the only cells to which the reference product will bind. Such binding eliminates the gland's ability to produce LH and FSH and thus renders the gland sterile. Sex steroid dependent tumors respond to such hormonal manipulation which in turn controls their growth. Growth is controlled because of the lack of steroidal hormones that would otherwise be secreted.

By way of contrast, the product of the instant invention acts directly on the tumor cells. The product of this invention binds directly to the tumor cells and kills them.

While it is certainly agreed that the intended use of a product does not avoid the anticipatory effect of a reference and is therefor does not directly affect the grounds for patentability of that product, the manner in which the product acts is evidence of there being a difference in the claimed product as compared to the reference product. The manner in which a product acts is therefore strong evidence on the subject of novelty and unobviousness. If the claimed product and the reference product act differently under substantially the same circumstances, they are probably not the same product, even though they may have the same superficial name and even though they may have been made using the same raw materials. Importantly, the claims of this application call for the fusion of a portion only of a specific protein, whereas the reference reports chemical reaction between a whole protein. This functional property of the instant claimed product, and its distinction from the functional property of the reference compound, even though both products have been made from similar starting materials, represents an avoidance of anticipation by the reference. How these different materials function also shows novelty and non-obviousness. It is therefore believed that this rejection should be withdrawn.

In the outstanding action, the examiner has contended that the instant claimed invention is anticipated by the disclosure of the Lombardo et al. reference. Again, the examiner contends that the method of making a product, and its intended use are not factors that lend patentability to that claimed product. As previously stated, the examiner's assertions are certainly generic truisms. The **identical** product does not become patentable because it is made in a different manner or is used for a different purpose. However, merely having the same superficial name does not end the inquiry as to identity of the claimed material with the prior art disclosed material. Even having been made from the same, or similar, starting compounds does not end the inquiry into anticipation. One must also look at the manner in which a product behaves because this is part and parcel of the nature of the compound being claimed and therefore this information has a bearing on whether they are indeed the same products regardless of its superficial name. The manner in which a product acts is evidence that bears on a determination of the identity of that product with a product that appears to be disclosed in a reference. That is not to say that the discovery of a new and unobvious use of a product makes that product patentable. It isn't that the discovery of a new use makes a previously known product patentable, it is the fact that when a product behaves in a manner that is substantially different from the way in which the prior art product behaves, that is good evidence that the prior art product is different from the current product. Similarly, the manner in which a product behaves has a bearing on whether that product is obvious from a consideration of the state of the prior art. If a product behave in an unexpectedly different manner, it is not obvious over the state of the prior art. This is so even if the new and old products have the same superficial name and even if they are both made from the same raw materials.

In paragraph 12 of the outstanding action, the examiner has objected to the claims of the instant application on the basis that they are allegedly not enabled by the instant specification. The examiner has conceded that the instant specification is quite enabling for an invention as claimed herein provided that definition of the ligated portions of the claimed molecules is

substantially reduced in scope. The examiner seems to be saying that the specification must mention and exemplify each and every species that falls within a claimed invention for the claim to be commensurate in scope with the enablement set forth in the specification. That is not the law!

The specification is a teaching document. Under 35 USC 112, it is required to disclose the whole of the invention in sufficient detail to enable a person of ordinary skill in the art to practice the invention. Certainly, it has never been held by any court or board that each and every species must be set forth and exemplified. What is required is that to be claimed, a genus, that is reasonably consistent with the disclosed species, must be exemplified by a sufficient number of species to strongly suggest that the genus is operative over its entire scope. Just how many species is needed to support the claiming of a genus is an indeterminate number that must be evaluated as to each case. In the instant situation, the materials that make up the operative compound are *per se* well known. Many variations of these compounds are well known. The general uses of these compounds is well known. What is new and patentable here is the fact that the two starting molecules can be ligated to form a new molecule that has two very valuable assets. The prior art that has been cited does not disclose a molecule that has both of these valuable assets In this case, the specification has ample teaching of the functional operation of the moieties of this invention. A cell killing moiety is ligated to an adenocarcinoma cell targeting moiety to make a new, genetically engineered molecule that will find and destroy adenocarcinoma cells in mammals. The specification sets forth examples of such entities and their positive effect on such cells. The functions of the fragments that have been ligated together are set forth in the claims. Other compounds that do not perform these functions are excluded from the claims. An example of the best mode contemplated by the inventors for carrying out the invention is set forth in the specification. 35 USC 112 requires no more. The examiner's rejections are therefore misplaced. It is urged that the examiner withdraw the objections raised in paragraph 12.

Note that claim 7 has been amended as suggested by the examiner. Note that claim 1 has also been amended in conformance with the examiner's suggestions.

In paragraphs 13 and 14 of the outstanding action, the examiner has rejected the patentability of claims 1, 2 and 7 as being anticipated by the disclosure of the Nett et al published application (WO 90/09799). In paragraph 15, these same claims are rejected as being anticipated by the cited Lombardo et al. published application (WO 93/15751). In paragraph 16, the same claims are rejected as being anticipated by the disclosure of the cited Rusieki et al. publication. All of these rejections are based on substantially the same theory. In each case, the examiner has attributed to the reference a disclosure of conjugating GnRH to a toxin. It has been pointed out above, and it is here reiterated, that the method by which the targeting moiety and the cell killing moiety are assembled is very important to distinguishing the compounds actually disclosed by the references from the compounds being claimed herein. The instant claimed product chimeras are different biological molecules as compared to the molecules disclosed in the references because they have been made in a different way and because they start from different starting molecules. In the instant invention, the targeting moiety is an oligonucleotide encoding 10 amino acids of GnRH or it is an analog. The references do not disclose such a starting material. The cell killing moiety is a mutated or truncated form of the toxin molecule. Ligating such modified compounds together is not disclosed in the prior art. The fact that such a ligated structure has the desired effect of targeting and killing adenocarcinoma cells is not disclosed in the prior art. Therefore, the references do not disclose the instant claimed products. The anticipation rejections must be withdrawn.

NOT Claims (1)

The examiner contends that the method of making the molecule is not to be considered when determining the identity of molecules made by different techniques. That is surely a truism. However, as has been pointed out above, where the claimed molecule is a reaction product of two different moieties, and these moieties can be assembled in different ways

depending on the process by which they are made, the method of making the claimed molecule must be taken into consideration when evaluating anticipation.

The molecules being joined to make the claimed molecules have numerous binding sites. The conditions employed in joining the reactant molecules together determine where the reactant molecules join each other. Where they join each other determines their chemical characteristics. Therefore, even though the references and the instant claims both are directed to the reaction products produced by joining a cell targeting moiety, illustrated by GnRH, and a cell killing moiety illustrated by PE (modified or mutated), these reaction products are not necessarily the same. One must look deeper into the situation to determine whether the claimed molecule is indeed the same as the molecules that are disclosed by the references. As has been pointed out above, when the ways in which these molecules behave after formation are taken into consideration, it is clear that the molecules that are disclosed by the references are not the same as the molecules being claimed herein. For that reason the anticipation rejection must fall and its withdrawal is solicited.

It is recognized that the examiner has stated that the use of a compound cannot make patentable what is otherwise anticipated. That is certainly true. The use to which it is desired to put the instant claimed molecules is not what separates these compounds from the prior art. It is the properties of these claimed molecules. The CAFC has repeatedly held that a chemical compound is defined by much more than its name and its empirical or structural formula. It is also defined by its properties. Those properties include how the molecule reacts. If the prior art molecule (that is a reaction product of A and B) has substantially different properties than the instant claimed reaction product of these same moieties A and B, and it is clear that the reaction that produces the instant claimed product is different from the reaction that produced the reference's product, the fact that the same reactants were employed in each case is completely unimportant and misleading.

The claimed compounds must be considered along with how they behave. The instant products attack and kill adenocarcinoma cells, that also include non-hormone dependent tumors. The reference materials attack and kill only sex-dependent tumors. It should be clear from this information that these are not the same compounds, even though they may have been made from the same nominal starting materials. Therefore, the rejection based on an anticipation theory cannot be sustained and must be withdrawn.

In paragraphs 17 and 18 of the outstanding action, the examiner has rejected the patentability of claims 3, 4 and 21 as being directed to subject matter that would have been obvious to a person of ordinary skill in the art at the time that the invention was made. The contention by the examiner is that each piece of the instant claimed molecule is known in the prior art and that therefore it would have been obvious to combine the two pieces to from the claimed chimeric toxin. The position of the examiner is respectfully traversed. The claims of this application are not for just any combination of any targeting hormone and any cell killing moiety made in any manner. The claims are directed to a GnRH analog **ligated** to a mutated toxin. That is simply not disclosed in the art. It has been pointed out above in what ways the instant claimed chimeric toxins differ from the molecules disclosed in the prior art. The results achieved emphasize the differences in the product molecules themselves. It is clear that a person of ordinary skill in this art, having the references before him would not employ a GnRH analog and would not employ a mutated toxin and would not ligate these together. That is the essence of non-obviousness.

It is therefore urged that the examiner reconsider and withdraw his rejection of the patentability of the claims of the instant application. It is particularly noted that claims 5, 6, 9

and 10 have not been rejected over the state of the art. At least these claims should be indicated to be allowable.

Respectfully submitted,
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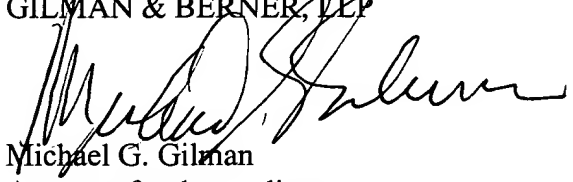

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